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PCT/SE99/00347

PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF THE RECORDING OF A CHANGE

(PCT Rule 92bis.1 and Administrative Instructions, Section 422)

To:

LARFELDT, Helene
Bergenstråhle & Lindvall AB
P.O. Box 17704
S-118 93 Stockholm
SUÈDE

Date of mailing (day/month/year) 04 October 2000 (04.10.00)	
Applicant's or agent's file reference HeL/GB 40769	**IMPORTANT NOTIFICATION**
International application No. PCT/SE99/00347	**International filing date** (day/month/year) 08 March 1999 (08.03.99)

1. The following indications appeared on record concerning:

[X] the applicant [ ] the inventor [ ] the agent [ ] the common representative

Name and Address	State of Nationality	State of Residence
SCOTIA LIPIDTEKNIK AB P.O. Box 6686 S-113 84 Stockholm Sweden	SE	SE
	Telephone No.	
	Facsimile No.	
	Teleprinter No.	

2. The International Bureau hereby notifies the applicant that the following change has been recorded concerning:

[X] the person [X] the name [X] the address [X] the nationality [X] the residence

Name and Address	State of Nationality	State of Residence
SCOTIA HOLDINGS PLC Scotia House Castle Business Park Stirling FK9 4TZ United Kingdom	GB	GB
	Telephone No.	
	Facsimile No.	
	Teleprinter No.	

3. Further observations, if necessary:

4. A copy of this notification has been sent to:

[X] the receiving Office
[ ] the International Searching Authority
[ ] the International Preliminary Examining Authority
[ ] the designated Offices concerned
[X] the elected Offices concerned
[ ] other:

The International Bureau of WIPO **34, chemin des Colombettes** **1211 Geneva 20, Switzerland**	Authorized officer I. Britel
Facsimile No.: (41-22) 740.14.35	Telephone No.: (41-22) 338.83.38

PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF ELECTION

(PCT Rule 61.2)

To:

Assistant Commissioner for Patents
United States Patent and Trademark Office
Box PCT
Washington, D.C.20231
ÉTATS-UNIS D'AMÉRIQUE

in its capacity as elected Office

Date of mailing (day/month/year) 09 December 1999 (09.12.99)	
International application No. PCT/SE99/00347	**Applicant's or agent's file reference** HeL/GB 40769
International filing date (day/month/year) 08 March 1999 (08.03.99)	**Priority date** (day/month/year) 06 March 1998 (06.03.98)
Applicant CARLSSON, Anders et al	

1. The designated Office is hereby notified of its election made:

[X] in the demand filed with the International Preliminary Examining Authority on:
01 October 1999 (01.10.99)

[ ] in a notice effecting later election filed with the International Bureau on:

2. The election [X] was

[ ] was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland	Authorized officer C. Cupello
Facsimile No.: (41-22) 740.14.35	Telephone No.: (41-22) 338.83.38

16

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
HeL/UB 40769		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/SE99/00347	08.03.1999	06.03.1998
International Patent Classification (IPC) or national classification and IPC7		
A 61 K 9/107, A 61 K 7/00, A 61 K 47/00		
Applicant		
Scotia LipidTeknik AB et al		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 4 sheets, including this cover sheet.

   ☒ This report is also accompanied by ANNEXES, i.e., sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 2 sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☐ Priority
   - III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
01.10.1999	03.07.2000
Name and mailing address of the IPEA/SE Patent- och registreringsverket Box 5055 S-102 42 STOCKHOLM Telex 17978 PATOREG-S Facsimile No. 08-667 72 88	Authorized officer Anneli Jönsson/EÖ Telephone No. 08-782 25 00

Form PCT/IPEA/409 (cover sheet) (January 1994)

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.
PCT/SE99/00347

I. Basis of the report

1. This report has been drawn on the basis of *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments.)*:

☐ the international application as originally filed.

☒ the description, pages 1-20, as originally filed,
pages _____, filed with the demand,
pages _____, filed with the letter of _____,
pages _____, filed with the letter of _____.

☒ the claims, Nos. _____, as originally filed,
Nos. _____, as amended under Article 19,
Nos. _____, filed with the demand,
Nos. 1-12, filed with the letter of 20.06.2000,
Nos. _____, filed with the letter of _____.

☒ the drawings, ~~sheets~~/fig --, as originally filed,
~~sheets~~/fig _____, filed with the demand
~~sheets~~/fig _____, filed with the letter of _____,
~~sheets~~/fig _____, filed with the letter of _____.

2. The amendments have resulted in the cancellation of:

☐ the description, pages _____
☐ the claims, Nos. _____
☐ the drawings, ~~sheets~~/fig _____

3. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the supplemental Box (Rule 70.2(c)).

4. Additional observations, if necessary:

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.
PCT/SE99/00347

V. Resoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Claims	1-12	YES
	Claims		NO
Inventive step (IS)	Claims		YES
	Claims	1-12	NO
Industrial applicability (IA)	Claims	1-12	YES
	Claims		NO

2. Citations and explanations

The claimed invention relates to the use of a topical formulation of oil-in-water emulsion type. The used formulation is intended to be a pharmaceutical or cosmetic formulation and the used formulation comprises an oil phase, an emulsifier and an aqueous phase. The emulsifier is a glycolipid material.

The claims have been amended with the letter filed on 20 June 2000. The claims have been specified to claim the use of the formulation of oil-in-water emulsion type as a carrier for the preparation of a topical cream or lotion providing a prolonged local effect of an incorporated pharmaceutically or cosmetically active substance.

The document WO 95/20943 discloses an oil-in-water emulsion comprising the glycolipid galactolipid as an emulsifier. The galactolipids comprise at least 50% digalactosyl-diacylglycerol, as is the specified galactolipid in present claims 4-6. The cited emulsion comprises 0.1-10% galactolipid and 0.1-50% oil and can, according to claim 13 be administered topically. Thus, the formulation used in the invention according to the present application is known from the cited document. The composition according to the cited document can further comprise components such as flavouring agents, colorants, thickening agents, co-surfactants, preservatives, antioxidants, etc. Therapeutic components, such as dermatological drugs, can also be incorporated in the composition. However, the property to have a prolonged

.../...

Supplemental Box
(To be used when the space in any of the preceding boxes is not sufficient)

Continuation of: V

local effect of an incorporated pharmaceutically or cosmetically active substance is not disclosed from the document. As the composition used in the present application is the same as the compositions known from the cited document, it would be obvious that the new effect, the prolonged local effect, would be obtained by the previous known composition. Moreover, the experimental tests in the present application show different compositions comprising different oils and galactolipids. The application reveals that the prolonged effect is dependent on the choice of oil. It would be obvious to a person skilled in the art to choose suitable components to the composition to get a composition with a prolonged local effect. The claims of the present application do not reveal the importance to choose special oil. It would also be obvious to a person skilled in the art to incorporate the substances claimed in claims 9-12 as it is known from the cited document to incorporate active substances in the known composition. Therefore, the claimed invention according to claims 1- 12 is not considered to involve an inventive step. However, the invention is considered to fulfil the requirements of novelty and industrial applicability.

From EP 647 443 A1 an oil-in-water emulsion is known. The composition comprises an oil-phase, comprising organopolysiloxanes, mineral oil, organic oil, synthetic oil or a vegetable oil. Suitable emulsifiers are glucose-fattyacid esters, alkylglucosefattyacid esters and at least one saccharose fattyacid ester, i.e. a glycolipid. The compositions comprise 5-50 % oil phase, preferably 10-30% and 1-10% of the emulsifier. The document does not disclose any composition with a prolonged local effect. The document only discloses the general state of the prior art.

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference HeL/UB 40769	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. PCT/SE99/00347	International filing date *(day/month/year)* 08.03.1999	Priority date *(day/month/year)* 06.03.1998
International Patent Classification (IPC) or national classification and IPC7 A 61 K 9/107, A 61 K 7/00, A 61 K 47/00		
Applicant Scotia LipidTeknik AB et al		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 4 sheets, including this cover sheet.

   ☒ This report is also accompanied by ANNEXES, i.e., sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 2 sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☐ Priority
   - III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
01.10.1999	03.07.2000
Name and mailing address of the IPEA/SE Patent- och registreringsverket Box 5055 S-102 42 STOCKHOLM Telex 17978 PATOREG-S Facsimile No. 08-667 72 88	Authorized officer Anneli Jönsson/EÖ Telephone No. 08-782 25 00

Form PCT/IPEA/409 (cover sheet) (January 1994)

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.
PCT/SE99/00347

I. Basis of the report

1. This report has been drawn on the basis of *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments.)*:

☐ the international application as originally filed.

☒ the description, pages 1-20, as originally filed,
pages _____, filed with the demand,
pages _____, filed with the letter of _____,
pages _____, filed with the letter of _____.

☒ the claims, Nos. _____, as originally filed,
Nos. _____, as amended under Article 19,
Nos. _____, filed with the demand,
Nos. 1-12, filed with the letter of 20.06.2000,
Nos. _____, filed with the letter of _____.

☒ the drawings, ~~sheets~~/fig --, as originally filed,
~~sheets~~/fig _____, filed with the demand
~~sheets~~/fig _____, filed with the letter of _____,
~~sheets~~/fig _____, filed with the letter of _____.

2. The amendments have resulted in the cancellation of:

☐ the description, pages _____
☐ the claims, Nos. _____
☐ the drawings, ~~sheets~~/fig _____

3. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the supplemental Box (Rule 70.2(c)).

4. Additional observations, if necessary:

V. Resoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Claims	1-12	YES
	Claims		NO
Inventive step (IS)	Claims		YES
	Claims	1-12	NO
Industrial applicability (IA)	Claims	1-12	YES
	Claims		NO

2. Citations and explanations

The claimed invention relates to the use of a topical formulation of oil-in-water emulsion type. The used formulation is intended to be a pharmaceutical or cosmetic formulation and the used formulation comprises an oil phase, an emulsifier and an aqueous phase. The emulsifier is a glycolipid material.

The claims have been amended with the letter filed on 20 June 2000. The claims have been specified to claim the use of the formulation of oil-in-water emulsion type as a carrier for the preparation of a topical cream or lotion providing a prolonged local effect of an incorporated pharmaceutically or cosmetically active substance.

The document WO 95/20943 discloses an oil-in-water emulsion comprising the glycolipid galactolipid as an emulsifier. The galactolipids comprise at least 50% digalactosyl-diacylglycerol, as is the specified galactolipid in present claims 4-6. The cited emulsion comprises 0.1-10% galactolipid and 0.1-50% oil and can, according to claim 13 be administered topically. Thus, the formulation used in the invention according to the present application is known from the cited document. The composition according to the cited document can further comprise components such as flavouring agents, colorants, thickening agents, co-surfactants, preservatives, antioxidants, etc. Therapeutic components, such as dermatological drugs, can also be incorporated in the composition. However, the property to have a prolonged

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Supplemental Box
(To be used when the space in any of the preceding boxes is not sufficient)

Continuation of: V

local effect of an incorporated pharmaceutically or cosmetically active substance is not disclosed from the document. As the composition used in the present application is the same as the compositions known from the cited document, it would be obvious that the new effect, the prolonged local effect, would be obtained by the previous known composition. Moreover, the experimental tests in the present application show different compositions comprising different oils and galactolipids. The application reveals that the prolonged effect is dependent on the choice of oil. It would be obvious to a person skilled in the art to choose suitable components to the composition to get a composition with a prolonged local effect. The claims of the present application do not reveal the importance to choose special oil. It would also be obvious to a person skilled in the art to incorporate the substances claimed in claims 9-12 as it is known from the cited document to incorporate active substances in the known composition. Therefore, the claimed invention according to claims 1- 12 is not considered to involve an inventive step. However, the invention is considered to fulfil the requirements of novelty and industrial applicability.

From EP 647 443 A1 an oil-in-water emulsion is known. The composition comprises an oil-phase, comprising organopolysiloxanes, mineral oil, organic oil, synthetic oil or a vegetable oil. Suitable emulsifiers are glucose-fattyacid esters, alkylglucosefattyacid esters and at least one saccharose fattyacid ester, i.e. a glycolipid. The compositions comprise 5-50 % oil phase, preferably 10-30% and 1-10% of the emulsifier. The document does not disclose any composition with a prolonged local effect. The document only discloses the general state of the prior art.

PCT/ SE 99/ 00347
20 -06- 2000

CLAIMS

1. Use of a formulation of the oil-in-water emulsion type comprising an oily material, an aqueous phase and a galactolipid material as an emulsifier, as a carrier for the preparation of a topical cream or lotion providing a prolonged local effect of an incorporated pharmaceutically or cosmetically active substance.

2. Use according to claim 1, wherein the formulation comprises 0.1-50 % by weight of oily material and 0.5-20 % by weight of emulsifier.

3. Use according to claim 1 or 2, wherein the formulation comprises 1-40 % by weight of oily material and 0.5-10 % by weight of emulsifier.

4. Use according to any of claims 1-3, wherein the galactolipid material consists of at least 50 % by weight of digalactosyl-diacylglycerols and a remainder of other polar lipids, and constitutes an amount of 1.0-5.0 % by weight of the formulation.

5. Use according to any of claims 1-4, wherein the galactolipid material consists of 50-70 % by weight of digalactosyldiacyl-glycerols and 30-50 % by weight of other polar lipids.

6. Use according to any of claims 1-3, wherein the galactolipid material is a fractionated oat oil which consists of at least 15 % by weight of digalactosyldiacylglycerols and a remainder of other polar and non-polar lipids, and constitutes an amount of 2.0-10 % by weight of the formulation.

7. Use according to any of claims 1-3 and 6, wherein the galactolipid material is a fractionated oat oil which contains 40-60 % by weight polar lipids and a remainder of non-polar lipids.

8. Use according to any of claims 1-7, of a cream base, comprising, in % by weight

Oily material	10.0-30.0 %
Galactolipid emulsifier	0.5-5 %
Thickener	2.0-10.0 %
Preservative	0.1-1.0 %
Water	ad 100 %

9. Use according to any of clains 1-8 for the preparation of a topical cream or lotion, incorporating a moisturiser, especially glycerol, as the active substance.

10. Use according to any of claims 1-9 for the preparation of a medicament for prophylaxis or treatment of atopic dermatitis.

11. Use according to any of claims 1-8 for the preparation of a topical cream or lotion, incorporating a corticosteroid as the active substance, for treatment of skin inflammation.

12. Use according to any of claims 1-8, for the preparation of a topical anti-psoriatic cream or lotion, incorporating 13-hydroxy-linoleic acid as the active substance.

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PATENT COOPERATION TREATY

PCT

REC'D 20 MAR 2001
WIPO PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
F 2037-1 WO		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/SE00/00347	22/02/2000	26/02/1999
International Patent Classification (IPC) or national classification and IPC C07D277/68		
Applicant ASTRAZENECA AB		

RECEIVED
JUN 20 2001
TECH CENTER 1600/2900

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 5 sheets, including this cover sheet.

   ☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☐ Priority
   - III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations suporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☒ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
23/08/2000	15.03.2001
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer Gregoire, A Telephone No. +49 89 2399 2994

Form PCT/IPEA/409 (cover sheet) (January 1994)

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/SE00/00347

I. Basis of the report

1. This report has been drawn on the basis of *(substitute sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments (Rules 70.16 and 70.17).)*:
Description, pages:

1-10 as originally filed

Claims, No.:

1-14 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in written form.
- ☐ filed together with the international application in computer readable form.
- ☐ furnished subsequently to this Authority in written form.
- ☐ furnished subsequently to this Authority in computer readable form.
- ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☐ the claims, Nos.:
- ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-14
	No:	Claims	
Inventive step (IS)	Yes:	Claims	1-4, 7, 11-12
	No:	Claims	5-6, 8-10, 13-14
Industrial applicability (IA)	Yes:	Claims	1-14
	No:	Claims	

2. Citations and explanations
see separate sheet

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:
see separate sheet

Re Item V

Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1) Reference is made to the following documents :

D1: WO-A1-9324473
D2: US-A-5763465
D3: US-A-5648370
D4: 'Dual D2-Receptor and beta2-Adrenoceptor Agonists for the Treatment of Airway Diseases. 1. Discovery and Biological Evaluation of some 7-(2-Aminoethyl)-4-hydroxybenzothiazol-2(3H9-one Analogues','ROGER V. BONNERT ET AL.','J. MED. CHEM.,','',41/25/00-00-1998,4915-4917,

2) Novelty (Art. 33 (1) and (2) PCT) :

The process described in Claims 1-7 can be considered as novel since no prior art document explicitly cites the intermediate III as starting material to obtain the desired compound.
Claims 8, 9, 10, 11 and 12 are new since neither compound IV nor its way of preparation are specifically disclosed in the prior art (carboxylate as leaving group is not mentioned therein).
Claims 13 and 14 referring to intermediates also not specifically disclosed in the prior art can be considered as novel.
The present application therefore fulfills the requirement of Art. 33 (2) PCT.

3) Inventive Step (Art. 33 (1) and (3) PCT) :

The technical problem underlying the present application is the provision of an alternative process for the preparation of a specific compound (formula (I)).
Prior art document D1-D4 report the synthesis of this compound (e. g. example 6 of D1) through an amide formation from the amino derivative of formula (II) and a corresponding carboxylic derivative. This amide function is then hydrogenated to lead to the desired compound (I).
The present invention relates to the addition of amine (II) on an alkene derivative

of formula (III). Since this can be considered as inventive for the skilled in the art and example 4-b) shows the efficacy of this pathway, inventive step can be acknowledged for claims 1-4. The examples provided to support claims 5-6 are nevertheless not convincingly showing that the alkene derivative is in situ obtained in such a one step procedure. The applicant indeed uses a different base (Et_3N instead of DBU) in examples 5, 6 or 7 and D1 relates the possibility of removing a leaving group from a similar compound (general formula III) with amine (II) in the presence of e. g. Et_3N in order to obtain the desired compound. Claim 7 is inventive since nothing was indicated about the mentioned compound but not that of Claim 8 which falls in the general formula III of D1. The use of this compound was clearly suggested for the preparation of the desired final same product. Claims 9 and 10 are not considered as inventive regarding e. g. D1 stating that compound III p. 2 can be prepared by known techniques (see also line 22-23 p. 3). The oxidation of sulfure into sulfoxide is similarly obvious e. g. from example 6 referring to step example 1-b). Claim 11 can be considered as inventive since no prior art suggest this addition step, rendering Claim 12 inventive as well. Claims 13 and 14 are not inventive since these compounds are suggested from D1.

Re Item VIII

Certain observations on the international application

The term "optionally" used in Claim 1 should be specified therein according to the description (Art. 6 PCT).

Claim 5 does not contain all technical essential features as required by Art. 6 PCT (see also Guidelines III-4.4). The starting material from which compound of formula (III) is formed is not mentioned.

PCT

WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 :
A61K 9/107, 7/00, 47/00

A1

(11) International Publication Number: WO 99/44585

(43) International Publication Date: 10 September 1999 (10.09.99)

(21) International Application Number: PCT/SE99/00347

(22) International Filing Date: 8 March 1999 (08.03.99)

(30) Priority Data:
9800729–7 6 March 1998 (06.03.98) SE

(71) Applicant *(for all designated States except US)*: SCOTIA LIPIDTEKNIK AB [SE/SE]; P.O. Box 6686, S–113 84 Stockholm (SE).

(72) Inventors; and
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(57) Abstract

The invention relates to the use of a topical formulation of the oil–in–water type comprising an oily material, an aqueous phase and an emulsifier, wherein the emulsifier is a galactolipid material, as a carrier for providing a prolonged effect of an incorporated active substance. New topical formulations are also described.

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TOPICAL FORMULATION OF THE OIL-IN-WATER TYPE, COMPRISING GALACTOLIPID MATERIAL AS EMULSIFIER, WITH A PROLONGED EFFECT OF AN INCORPORATED ACTIVE SUBSTANCE

The present invention refers to a topical formulation of the oil-in-water emulsion type, in which a variety of pharmaceutical or cosmetic compounds can be incorporated, and which after application on the skin gives a prolonged local effect of the incorporated compound.

BACKGROUND OF THE INVENTION

Dermatological formulations for topical administration, such as creams, lotions, ointments and gels, are used in pharmacy, medicine and cosmetics for curative and prophylac- tic treatment of different conditions. It is in general desirable that said formulation brings about a prolonged effect.

There are different areas where there is a continuous need of an improved, that is long lasting, topical treatment as exemplified below.

- People with very dry skin such as atopic dry skin and people who frequently are exposed to water and soap and thus often develop dry skin conditions need to apply a protective cream or ointment to their skin. Examples of people frequently exposed to water and soap are doctors and nurses who must wash their hands and face before examining patients, workers who are handling paints and grease and often need to use strong detergents to clean their hands, and, most common of all, home workers. For these and other categories of people having dry skin conditions a cream or lotion with an extended effect on skin smoothing and moisturising would be preferred.

- The use of hydrocortisone and other steroidal creams is very common in the treatment of local inflammatory conditions in the skin. The systemic absorption of the steroid potentially gives unwanted side-effects. A cream with a sustained release of the active steroid could increase the local effect and decrease the systemic absorption, a very much preferred therapeutic situation, especially in small children.

- The treatment of Athlete's foot or other fungal

infections with topical antifungal or of many skin infec- tions with antibiotics or antivirals requires twice or three times daily applications of the cream or gel to be effective. A once-daily formulation would certainly improve compliance, effectiveness, as well as comfort during treatment.

- The treatment of any other skin condition, including psoriasis, eczemas, other inflammatory disorders, cancers, precancerous conditions, ageing, wrinkling, ultraviolet radiation damage and any other condition which may respond to a topically applied therapeutic agent.

Preferred topical formulations are creams and lotions, that is typically oil-in-water emulsions which spread readily on the skin, leave no detectable residue and adhere to the treated area without being tacky. Said emulsions normally consist of an oil phase, an aqueous phase and an emulsifier. Ointments, which mainly comprises an oil phase, are greasy and form a greasy film on the skin preventing moisture loss. Gels which might be liposomal preparations do not contain any oil. Topical preparations of the oil-in-water emulsion type are generally more appreciated by the user from a cosmetic point of view, but have not previously been claimed to give any extended effect of incorporated substances of dermatological or cosmetological interest. From a dermatological standpoint oil-in-water emulsion type formulations are often preferred, particularly if the number of ingredients can be reduced to a minimum.

PRIOR ART

Highly structured vehicles, such as inversed hexagonal and cubic liquid crystals, may exhibit sustained-release properties, either by binding the water or by stiffening the amphiphilic film within the formulation, see Osborne, D.W., et al. in Drugs and the Pharmaceutical Sciences, Swarbrick J.(ed.), Vol. 42 (1990), pp. 374-379. Drug formulations containing liposomes for topical use may give a sustained local effect of the incorporated compound, see Korting, H.C., et al. in J. Am. Acad. Dermatol., Vol. 25 (1991), pp. 1068-1071. The topical drug

delivery systems described are, however, far more complicated lipid preparations than a topical cream of the oil-in-water emulsion type. For reasons of stability of topical liposomal systems, most authors have proposed a gel base. Gel formulations are, however, more likely to produce side effects than cream or ointment preparations.

WO 95/03784, Insite Vision Inc., discloses a cross-linked polymeric medicament delivery system containing an interactive agent associated with the polymer, which is said to slow release of medicament out of the system. The system can be used in dermal formulations but is particularly useful as topical ophthalmic delivery systems. This invention does not relate to any slow release effects of the cream, but on polymeric systems included in the cream. The slow release effects in this system can be ascribed to the polymeric system.

Topical creams of the oil-in-water emulsion type have not previously been reported as having potential sustained release properties. However, there is a need for topical sustained release formulations, such as oil-in-water emulsions, which are uncomplicated with respect to compositional design as well as manufacturing. Furthermore, less complicated formulations have a major advantage in that they are less likely to cause irritant or hypersensitivity reactions and hence to be more acceptable as skin care preparations for therapeutic or cosmetic use.

WO 95/20943, Karlshamns LipidTeknik AB, discloses an oil-in-water emulsion comprising 0.01-50 % by weight of a galactolipid material as an emulsifier. Said emulsion is said to be useful as a carrier for active substances in a pharmaceutical composition but also in nutritional, cosmetic, food and agricultural products. The emulsions do not exhibit any unpleasant odour or taste and are stable towards oxidation. There is, however, nothing stated about an optional sustained effect.

DESCRIPTION OF THE INVENTION

The present invention relates to an oil-in-water

emulsion for topical application to the skin comprising an emulsifier, an oil phase, and an aqueous phase, into which cosmetic or pharmaceutical substances can be incorporated for the local treatment of various skin conditions and disorders.

It has surprisingly been found that a topical cream or lotion of the oil-in-water emulsion type, in which a galactolipid material is used as the emulsifier, and into which a variety of pharmaceutical or cosmetic compounds can be incorporated, after application on the skin gives a sustained local effect of the incorporated compound.

The present invention refers to a topical formulation of the oil-in-water emulsion type, in which a variety of pharmaceutical or cosmetic compounds can be incorporated, comprising an oily material, an emulsifier being a glycolipid based material, and an aqueous phase, and which after application on the skin gives a sustained local effect of the incorporated compound.

According to another aspect the invention refers to the use of a topical formulation of the oil-in-water type comprising an oily material, an aqueous phase and an emulsifier, wherein the emulsifier is a galactolipid material, as a carrier for providing a prolonged effect of an incorporated active substance.

Especially the invention refers to the use of a topical formulation, which can be a cream or a lotion, comprising 0.1-50 % by weight oily material, preferably 1-40 %, and 0.5-20 % by weight emulsifier.

No particular limitation is imposed on the oily material, that is the non-polar lipid material, of the formulation. Examples are vegetable oils, animal oils, fatty acids, synthetic oils, mineral oils, natural and synthetic glycerides, sterol esters, fatty alcohols, and other substances, including lipophilic drugs, obvious to a person skilled in the art, which can be emulsified using a polar lipid emulsifier.

Preferred oily materials to be emulsified are any fatty acid or a derivative thereof, such as vegetable oils of all

types, such as oils from the seeds and beans of soybean, sunflower, rapeseed (canola), palm, corn, evening primrose, borage, groundnut, sesame, and similar.

There are also synthetic or semi-synthetic glycerides, propanediol derivatives, cholesteryl esters, other esters and other appropriate lipid materials. Another oily material for the emulsion is a medium-chain triacylglycerol (MCT) oil.

There are also many lipids such as free fatty acids, mono-, di- and triacylglycerols, phospholipids, cholesterol esters and lipids and oils of many other types which have therapeutic actions in themselves, such as tea tree oil, and which may be advantageously formulated in the form of a topical cream or optionally lotion. In this case the therapeutically active substance is the oily material, which can also have other bioactive properties.

The emulsifier according to the invention should be a glycolipid, preferably a galactolipid based material. Galactolipids can be defined as glycosylglycerides based on galactose and are well known constituents of plant cell membranes. The most important classes of these contain one to four sugars linked glycosidically to diacylglycerol. The two most abundant classes contain one and two galactose units, respectively, and are commonly known as mono- and digalactosyldiacylglycerol, MGDG and DGDG. Galactolipids, primarily DGDG and DGDG-rich materials, have been investigated and found to be a surface active material of interest in industrial application such as food, cosmetics, and pharmaceutical applications.

Synthetic diglycosyldiacylglycerols based on galactose, optionally in combination with other monosaccharide units, such as glucose, semi-synthetic, and natural glycosylglycerides, isolated from any source, can be used in accordance with the invention.

An intrinsic beneficial feature of the galactolipids is the galactose units comprising the polar head group in each lipid molecule, which may sterically stabilise the emulsion droplets in an emulsion. The galactose groups may also interact strongly

with water and other polar substances, such as a water-soluble drug or a excipient, added to the emulsion.

WO 95/20943 describes the use of DGDG-rich material, a galactolipid material, as an emulsifier in oil-in-water emulsions. Said galactolipid material was prepared from cereals by extraction of the lipids with ethanol and a subsequent purification on a chromatographic column to pure DGDG or a DGDG-rich fraction of polar lipids. The galactolipid emulsifier consists of at least 50 % digalactosyldiacylglycerols and a remainder of other polar lipids and can be used as the galactolipid emulsifier of the invention, preferably in an amount of 1.0-5.0 % by weight. The galactolipid material for instance consists of 70-80 % DGDG and 20-30 % other polar lipids.

According to a preferred embodiment of the invention the galactolipid emulsifier consists of 50-70 % digalactosyldiacyl-glycerols and 30-50 % other polar lipids. This material is manufactured by Scotia LipidTeknik AB, Stockholm, as CPL®-Galactolipid (registered trade mark owned by Scotia Holdings plc). A preferred topical formulation of the invention comprises CPL®-Galactolipid as the galactolipid material.

WO 97/11141 describes a method for producing a fractionated vegetable oil which is characterised in containing 10-90 % by weight of polar lipids, preferably 20-75 %, and a remainder of non-polar lipids. Said fractionated vegetable oil can also be used as the galactolipid emulsifier of the invention, preferably in an amount of 2.0-10.0 % by weight. The fractionated vegetable oil preferably contains more than 5 % by weight, preferably more than 20 %, glycolipids and preferably more than 3 % by weight, preferably more than 15 %, DGDG.

According to a preferred embodiment of the invention the galactolipid material consists of 40-60 % polar lipids and a remainder of non-polar lipids. A fractionated oat oil of this composition consisting of a wide range of polar and amphiphilic lipids in a continuous triglyceride phase is manufactured by Scotia LipidTeknik AB, Stockholm, as Galactolec™. A preferred

topical formulation comprises Galactolec™ as the galactolipid material.

The galactolipid based emulsifier is a safe and non-toxic material for human and veterinary use. It is also an environmentally friendly material.

Topical formulations, such as creams and lotions, are prepared by using a polar lipid emulsifier either as the sole emulsifier or in combination with other amphiphilic compounds, that is co-surfactants. The formulation may also comprise optional additives known in the art for improving different aspects of the composition, such as thickening agents, preservatives, antioxidants, fragrance and the like.

The creams according to the invention are characterised by having excellent cosmetic properties. Furthermore, they contain a minimum number of ingredients, without any stabilising ingredients known to give irritation or sensitisation of the skin. Despite the low numbers of ingredients the creams are extremely stable, with shelf lives of several years.

The active substances can be either water soluble or oil soluble or amphiphilic, and can be any type of pharmaceutical or cosmetological ingredient suitable for topical preparations, such as moisturising agents, e.g. glycerol, propylene glycol, urea, vitamins, e.g. retinol and tocopheryl esters, anti-inflammatories, e.g. glucocorticosteroids such as hydrocortisone, hydrocortisone butyrate, chlobetasol, triamcinolone, fluticasone, momethasone and betamethasone, antibiotics, e.g. erythromycin, antivirals, e.g. acyclovir, antifungals, e.g. miconazole, antiseptics, e.g. cetrimide, agents for treating acne, e.g. tretinoin, benzylperoxide, psoriasis, e.g. dithranol and calcipotriol, senile pruritus, dry skin and wrinkles, cancer and pre-cancerous conditions, such as active keratosis, and UV protecting agents to be included in suntan creams and lotions.

Topical creams according to the invention are prepared by conventional methods. For example, a cream with 20 % by weight

of oil is prepared by adding the emulsifier to a triacylglycerol oil. The oil phase may also contain oil-soluble additives such as antioxidants and fragrance. The total emulsifier concentration is 1.5 % by weight. The oil phase is then gently mixed. The continuous phase may be pure water or an aqueous solution containing water-soluble additives such as glycerol, preservatives and buffers. A water-soluble active compound, such as glycerol as a moisturiser, may then be added to the aqueous phase; consequently, an oil-soluble compound such as 13-hydroxy-9,11-octadecadienoic acid (13-HODE) is added to the oil phase. Hydrocortisone, an anti-inflammatory drug which is insoluble in both water and oil, may be dispersed in either the aqueous phase or the oil phase. Alternatively, the drug may also be added to the final cream in an extemporaneous preparation. If necessary, the pH of the aqueous phase is adjusted. The oil phase as well as the aqueous phase are preheated to 70°C and then the oil phase is added to the aqueous phase under high-shear mixing. The pre-emulsion is then subjected to homogenisation at 200 psi. After cooling, the cream is transferred to suitable containers.

The invention also refers to the use of a topical formulation of the invention, wherein the incorporated compound is a moisturising compound for the preparation of a medicament for prophylaxis or treatment of atopic dermatitis.

Formulations, that is creams and lotions, having the following, preferred compositions can be prepared accordingly:

Topical cream base giving an incorporated substance a prolonged effect, comprising in % by weight

Oily material	10.0-30.0 %
Galactolipid emulsifier	0.5-5 %
Thickener	2.0-10.0 %
Preservative	0.1-1.0 %
Water	ad 100 %

Topical formulation having a prolonged moisturising effect, comprising in % by weight

Glycerol	1.0-5.0 %
Oily material	10.0-30.0 %
Galactolipid emulsifier	0.5-5 %
Thickener	2.0-10.0 %
Preservative	0.1-1.0 %
Water	ad 100 %

Topical formulation having a prolonged anti-inflammatory effect, comprising in % by weight

Hydrocortisone	0.5-1.5 %
Oily material	10.0-30.0 %
Galactolipid emulsifier	0.5-5 %
Thickener	2.0-10.0 %
Preservative	0.1-1.0 %
Water	ad 100 %

Topical formulation having a prolonged anti-inflammatory effect, comprising in % by weight

Betamethasone	0.01-0.5 %
Oily material	10.0-30.0 %
Galactolipid emulsifier	0.5-5 %
Thickener	2.0-10.0 %
Preservative	0.1-1.0 %
Water	ad 100 %

Topical formulation having a prolonged anti-psoriatic effect, comprising in % by weight

13-hydroxy-linoleic acid	0.001-0.1 %
Oily material	10.0-30.0 %
Galactolipid emulsifier	0.5-5 %
Thickener	2.0-10.0 %
Preservative	0.1-1.0 %
Water	ad 100 %

Different topical formulations with various non-polar oils as the cream base were formulated as described in Examples 1-7.

Typical batch sizes are 0.5 to 1 kg. All concentrations are expressed in percent by weight.

EXAMPLES OF FORMULATIONS

Example 1. Moisturising cream

Oil phase:		
CPL®-Soybean oil	20.0 %	Oily material
Cetostearyl alcohol	7.0 %	Thickener
Glyceryl monostearate/citrate	2.0 %	Thickener
Emulsifier:		
CPL®-Galactolipid	1.5 %	
Aqueous phase:		
Glycerol	2.0 %	Moisturiser
Methyl-p-hydroxybenzoate	0.54 %	Preservative
Propyl-p-hydroxybenzoate	0.06 %	Preservative
Water	ad 100 %	

The oil and CPL®-Galactolipid were mixed in a beaker and then stirred with a magnetic stirrer until the galactolipid material had dispersed, that is for 30-60 min. The aqueous phase was mixed in another beaker and stirred with a magnetic stirrer. When the oil phase was homogeneous glyceryl monostearate/ citrate and cetostearyl alcohol were added. The oil phase and the aqueous phase were both heated to 65-70°C while stirring. The warm oil phase was added to the warm aqueous phase during high-shear mixing (Polytron PT-MR 3000). After addition of the oil phase the pre-emulsification (high-shear mixing) continued for 2 minutes at 15,000 rpm. The pre-emulsion was then homogenised 2 times at 200 psi in an Ultrasonic homogeniser (Branson Minisonic 4). The cream was allowed to cool in a water bath.

Example 2. Moisturising lotion

Oil phase:		
CPL®-Evening Primrose oil	12.0 %	Oily material
Cetostearyl alcohol	2.0 %	Thickener
Glyceryl monostearate/citrate	2.0 %	Thickener
Ascorbyl palmitate	0.02 %	Antioxidant
Emulsifier:		

CPL®-Galactolipid	1.0 %	
Aqueous phase:		
Glycerol	2.0 %	Moisturiser
Methyl-p-hydroxybenzoate	0.54%	Preservative
Propyl-p-hydroxybenzoate	0.06%	Preservative
Fragrance	0.1 %	
Water	ad 100 %	

The lotion was prepared in the same way as the cream in Example 1, that is CPL®-Evening Primrose Oil, CPL®-Galactolipid and ascorbyl palmitate were mixed in a beaker and stirred until the galactolipid material had dispersed properly, that is for 30-60 minutes. The rest of the ingredients was added to the oil phase which was then heated to 70°C. The aqueous phase was prepared in another beaker and heated to 70°C. The oil phase was added to the aqueous phase during high-shear mixing. After addition of the oil phase the high-shear mixing, that is pre-emulsification, continued for 2 min at 15,000 rpm. The pre-emulsion was homogenized twice at 200 psi in an Ultrasonic homogeniser (Branson Minisonic 4). The lotion was allowed to cool in a water bath. The fragrance was added to the cool, that is 35°C, lotion.

Example 3. Moisturising cream

Oil phase:		
CPL®-Evening Primrose oil	20.0 %	Oily material
Cetostearyl alcohol	7.0 %	Thickener
Glyceryl monostearate/citrate	2.0 %	Thickener
Ascorbyl palmitate	0.02%	Antioxidant
Emulsifier:		
Galactolec™	3.0 %	
Aqueous phase:		
Glycerol	2.0 %	Moisturiser
Methyl-p-hydroxybenzoate	0.63%	Preservative
Propyl-p-hydroxybenzoate	0.07%	Preservative
Water	ad 100 %	

The cream was prepared as described in Example 1.

The cream had the following appearance in the microscope. Small regular to irregular droplets of uniform size evenly distributed in the sample. The average droplet size, estimated by comparison with a ruler installed in the microscope, was

found to be in the range of 5-10 μm.

Example 4. Cream base

Oil phase:		
Olive oil	20.0 %	Oily material
Cetostearyl alcohol	7.0 %	Thickener
Glyceryl monostearate	2.0 %	Thickener
Emulsifier:		
CPL®-Galactolipid	1.0 %	
Aqueous phase:		
Methyl-p-hydroxybenzoate	0.54 %	Preservative
Propyl-p-hydroxybenzoate	0.06 %	Preservative
Tri-sodium citrate dihydrate	0.035%	pH-modifier
Citric acid (aq.)	q.s. pH 3.5	pH-modifier
Water	ad 100 %	

The cream was prepared as described in Example 1.

Example 5. Cream base

Oil phase:		
Medium-chain triglyceride oil	10.0 %	Oily material
Cetostearyl alcohol	7.0 %	Thickener
Glyceryl monostearate	2.0 %	Thickener
Emulsifier:		
CPL®-Galactolipid	1.0 %	
Aqueous phase:		
Methyl-p-hydroxybenzoate	0.18 %	Preservative
Propyl-p-hydroxybenzoate	0.02 %	Preservative
Water	ad 100 %	

The cream was prepared as described in Example 1.

Example 6. Anti-inflammatory cream

Oil phase:		
Hydrocortisone	1.0 %	Active substance
CPL®-Evening Primrose oil	20.0 %	Oily material
Cetostearyl alcohol	7.0 %	Thickener
Glyceryl monostearate	2.0 %	Thickener
Ascorbyl palmitate	0.02 %	Antioxidant
Emulsifier:		
CPL®-Galactolipid	1.5 %	
Aqueous phase:		
Glycerol	2.0 %	Moisturiser
Methyl-p-hydroxybenzoate	0.63 %	Preservative

Propyl-p-hydroxybenzoate	0.07 %	Preservative
Water	ad 100 %	

Hydrocortisone was added to the mixture of oil and galactolipid. Otherwise the cream was prepared as described in Example 1.

Example 7. Anti-inflammatory cream

Oil phase:		
Betamethasone, dipropionate	0.05 %	Active substance
CPL®-Evening Primrose oil	20.0 %	Oily material
Cetostearyl alcohol	7.0 %	Thickener
Glyceryl monostearate	2.0 %	Thickener
Ascorbyl palmitate	0.02 %	Antioxidant
Emulsifier:		
CPL®-Galactolipid	1.5 %	
Aqueous phase:		
Glycerol	2.0 %	Moisturiser
Methyl-p-hydroxybenzoate	0.63 %	Preservative
Propyl-p-hydroxybenzoate	0.07 %	Preservative
Water	ad 100 %	

A comparable cream is obtained if betamethasone, dipropionate 0.05 % is replaced by betamethasone, valerate 0.1 %.

Example 8. Anti-psoriatic cream

Oil phase:		
13-HODE	0.01 %	Active substance
CPL®-Evening Primrose oil	20.0 %	Oily material
Cetostearyl alcohol	7.0 %	Thickener
Glyceryl monostearate	2.0 %	Thickener
Ascorbyl palmitate	0.02 %	Antioxidant
Emulsifier:		
CPL®-Galactolipid	1.5 %	
Aqueous phase:		
Methyl-p-hydroxybenzoate	0.63 %	Preservative
Propyl-p-hydroxybenzoate	0.07 %	Preservative
Water	ad 100 %	

A small amount, about 5 %, of the oil mixture was added to 13-HODE (13-hydroxy-linoleic acid, from Scotia Pharmaceuticals Ltd, Carlisle). This mixture was not heated like the rest of the oil phase and was added separately during the pre-emulsification

step. Otherwise the cream was prepared as in Example 1.

EXPERIMENTAL TESTS

Tests of skin smoothing and moisturising properties.

The aim of the studies was to evaluate the moisturising and smoothing properties of creams of the invention after use twice daily for 14 days. Twenty healthy female volunteers aged 18 to 60 years were studied.

The test creams had the following compositions:

	Cream A	Cream B	Cream C
Oil phase:			
CPL®-Evening Primrose oil	20.0 %	20.0 %	20.0 %
Cetostearyl alcohol	7.0 %	7.0 %	7.0 %
Ascorbyl palmitate	0.02 %	0.02 %	0.02 %
Emulsifier:			
CPL®-Galactolipid	0.75 %	0.75 %	1.5 %
Aqueous phase:			
Glycerol	-	2.0 %	2.0 %
Methyl-p-hydroxybenzoate	0.54 %	0.54 %	0.63 %
Propyl-p-hydroxybenzoate	0.06 %	0.06 %	0.07 %
Water	ad 100 %	ad 100 %	ad 100 %

All creams were prepared in the following way: The CPL®-Evening Primrose oil, CPL®-Galactolipid and ascorbyl palmitate were mixed in a beaker and then stirred with a magnetic stirrer until the galactolipid was completely dispersed, that is for 30-60 min. The aqueous phase was mixed in another beaker and stirred with a magnetic stirrer. When the oil phase was homogeneous, cetostearyl alcohol was added. The oil phase and the aqueous phase were both heated to 55°C while stirring. The warm oil phase was added to the warm aqueous phase during high-shear mixing (Polytron PT-MR 3000). After addition of the oil phase the pre-emulsification continued for 2 min at 15,000 rpm. The pre-emulsion was then homogenised 6 times at 200 psi in an Ultrasonic homogeniser (Branson Minisonic 4). The cream was allowed to cool in a water bath.

On the first day of the study the subjects were instructed as to the proper manner of application of the products. The creams were then applied by the subjects at home

once in the morning and once in the evening as part of the daily body care routine.

An amount approximating the usual applied amount of skin care cream (one fingertip full, approximately 0.2 ml) was taken from the respective container, applied to the test fields noted on the container and rubbed in with the finger. The test fields were not marked during the application period. In order to locate the test fields, the inside of the forearm was optically divided into thirds. The middle third was defined as the lower test field and the upper third as the upper test field. An area the width of two fingers was left free between the two test fields on the underarm. A field on the inside of the upper arm served as the upper test field. The subjects were given a stencil to simplify locating the boundary between the lower and middle field on each arm.

The subjects were instructed that the finger used to apply the creams had to be carefully cleaned with a dry cloth between applications to avoid mixing of the test preparations.

Skin moisture was assessed using a device for determining the capacitance of the skin surface (Corneometer CM 820, Courage & Khazaka, Cologne). The capacity of a conductor (the more or less moist stratum corneum on the skin surface) to store an electric charge is recorded using this method. The instrument probe was held onto the skin without pressing for a brief, defined interval. Five measurements were made per test field. The mean of the five measurements was recorded on-line.

Following the measurement of skin moisture, a negative replica of the skin was made using 2-component silicone rubber impression material (Xantopren® L, Fa. Bayer Dental, Leverkusen, Germany). The subjects laid the stretched but relaxed arms on special arm rests with the inner surface facing upwards. A surface of approximately 8 x 8 cm in the centre of the test fields was thinly covered with the impression mass mixed with hardener. Approximately 3 min were required for setting. The replicas were peeled off after 8 min. Labels were pressed into the lower edge of the hardening mass. These serve for

identification as well as marking of the alignment.

The surface of the silicone replicas was scanned using a Hommel-Tester T2000 (Hommelwerke, Schwenningen, Germany). The path and speed of scanning were controlled over the software. The surface was characterised by the roughness parameter $R_{z(DIN)}$. Each replica was measured in a star-shaped fashion in 12 directions (30° angles).

Skin moisture was measured and replicas taken immediately before the first application of treatments (baseline) and on study days 15, 16 and 17. The measurements on day 15 were performed 12 to 16 hours after the last application. The measurements on day 16 and 17 were performed 36 to 40 h and 60 to 64 h, respectively, after the last application. The silicone replicas were made directly following the corneometer measurements. The results are presented in Table 1 and 2.

Cream A did not lead to any improvement at all in skin moisture. The incorporation of an active moisturising agent (glycerol) in Cream B resulted in a clearly demonstrated moisturising effect as expected. Unexpectedly though, the effect was also long lasting.

Table 1. Skin moisturisation.

	Comparison	Moisturisation
Cream A (no active)	day 0 vs. day 15	-1.3 %
	day 0 vs. day 16	-0.9 %
Cream B (glycerol)	day 0 vs. day 15	+6.3 %**
	day 0 vs. day 16	+7.3 %**
Cream C (glycerol)	day 0 vs. day 15	+16.9 %**
	day 0 vs. day 16	+12.7 %**
	day 0 vs. day 17	+6.6 %**

*= p<0.1 ** = p<0.05

Table 2. Skin roughness.

	Comparison	Smoothing
Cream C (glycerol)	day 0 vs. day 15	+6.3 %*
	day 0 vs. day 16	+6.6 %**
	day 0 vs. day 17	+3.3 %*

*= p<0.1 ** = p<0.05

The sustained effect found for Cream B was even more pronounced for Cream C which contained a higher content of

the galactolipid based emulsifier. Conventional creams containing glycerol have not been reported to exhibit any sustained moisturising effect at all. The results presented in Table 1 and 2 clearly and surprisingly demonstrate a moisturising as well as a smoothing effect which last for at least three days after the last application.

The test of skin smoothing and moisturising properties of creams was repeated with slightly different cream compositions. The test creams had the following compositions:

	Cream D
Oil phase:	
CPL®-Evening Primrose oil	20.0 %
Cetostearyl alcohol	7.0 %
Glyceryl stearate	2.0 %
Ascorbyl palmitate	0.02 %
Emulsifier:	
CPL®-Galactolipid	1.5 %
Aqueous phase:	
Glycerol	2.0 %
Methyl-p-hydroxybenzoate	0.63 %
Propyl-p-hydroxybenzoate	0.07 %
Water	ad 100 %

In creams E, F and G the CPL® - Evening primrose oil was replaced by the same amount, i.e. 20 % of soybean oil, MCT oil and liquid paraffin oil, respectively. All other ingredients and the amounts of each were as in cream D.

Obviously the prolonged moisturising effect is dependent of the choice of oil as shown in Table 3 below. However, all four creams based on the oil-in-water emulsion type, described in the present invention, have a general ability of prolonging the moisturising effect compared to commercially available creams.

Table 3. Skin moisturisation

	Comparison	Moisturisation
Cream D	day 0 vs. day 15	+8.4 %**
(Evening primrose oil)	day 0 vs. day 16	+10.9 %**
	day 0 vs. day 17	+6.0 %**

Cream E (Soybean oil)	day 0 vs. day 15	+6.7 %**
	day 0 vs. day 16	+4.3 %
	day 0 vs. day 17	+1.7 %
Cream F (MCT oil)	day 0 vs. day 15	+8.8 %**
	day 0 vs. day 16	+6.3 %**
	day 0 vs. day 17	+5.8 %*
Cream G (Liquid paraffin oil)	day 0 vs. day 15	+7.2 %**
	day 0 vs. day 16	+6.5 %**
	day 0 vs. day 17	+2.4 %

* = $p<0.1$ ** = $p<0.05$

A consumer test

Thirty human volunteers participated in a consumer test of cream D described above. All subjects were regular users of emollients and moisturisers; eighteen subjects because of having atopic dry skin and twelve subjects because of necessary frequent exposure to detergents and water, e.g. during work at hospitals.

All subjects received one tube containing 100 ml of the cream and a questionnaire to fill in prior to, during and after having used the cream for two days.

The questionnaire was divided into six parts. The first part covered the background, sex, date of birth, the reason for and the frequency of using emollients etc. Parts two, three, four and five covered questions related to: the immediate reaction, 5-10 minutes later, after washing of hands, and after two days of using the cream, respectively. Part six covered "Further comments". In parts two, three, four and five, the question raised was, "To what extent do you agree with the following statements?" The extent of agreement could be given a score between 0 and 10, where 0 meant "No, not at all" and a score of 10 meant "Yes, definitely". For practical reasons the score results were grouped together according to the following:

0-2: No, not at all

3-7: Yes, to a certain degree

8-10: Yes, definitely

The moisturising effect was found to be more long lasting

than what is normally experienced with this type of products. It is also clear from the results presented in Table 4 that washing the skin is not detrimental to the effect, which is normally the case when using emollients and moisturisers. It makes it much easier to keep the skin smooth and supple and to avoid dryness. The cream was not found to be irritating to dry and sensitive skin. It seems to be very well tolerated also by persons with atopic dry skin.

Table 4.

To what extent do you agree with the following statements?

Statement / Extent of agreement	No. of subjects giving the score 0-2	3-7	8-10
Immediate reaction			
"The cream is easily absorbed into the skin"	3	13	14
"The cream is greasy on my skin"	10	14	5
"The odour of the cream is unpleasant"	22	7	1
"The cream irritates the skin"	30	0	0
"The skin feels smooth and supple"	1	4	25
5-10 minutes later			
"The cream is greasy on my skin"	24	4	2
"The odour of the cream is unpleasant"	22	5	1
"The skin feels smooth and supple"	0	6	24
"The skin is dry"	25	4	1
After washing of hands (with soap and water)			
"The skin still feels smooth and supple"	4	5	21
"The skin is dry again"	23	2	5
After two days of using the cream			
"I like the cream"	1	7	20
"The effect of the cream is long lasting"	4	8	16

A pilot study on children having atopic dry skin

The study was performed at two Swedish hospitals by dermatologists specialised in the field of atopic dermatitis. Twenty children were treated for two months with cream D described above. The age of the children varied between one and twelve years and they were all having widespread atopic dry skin, regularly developing into periods of acute atopic dermatitis. The dermatitis was treated in the normal way, i.e.

with glucocorticoids of varying potencies. Treatment with cream D was started at a stage with no acute dermatitis and the cream was applied only once daily at bedtime.

Preliminary results strongly indicate the potential of cream D with respect to its ability to decrease frequency as well as seriousness of the periods of atopic dermatitis. Furthermore, the previously necessary amounts of glucocorticosteroids used could be significantly reduced if cream D was used to prevent skin from being dry and sensitive.

CLAIMS

1. A topical formulation of the oil-in-water emulsion type, in which a variety of pharmaceutical or cosmetic compounds can be incorporated, comprising an oily material, an emulsifier and an aqueous phase, wherein the emulsifier is a glycolipid based material, and which after application on the skin gives a prolonged local effect of the incorporated compound.

2. A topical formulation according to claim 1, comprising 0.1-50 % by weight oily material and 0.5-20 % by weight galactolipid emulsifier.

3. Use of a topical formulation of the oil-in-water type comprising an oily material, an aqueous phase and an emulsifier, wherein the emulsifier is a galactolipid material, as a carrier for providing a prolonged effect of an incorporated active substance.

4. Use according to claim 3, wherein the topical formulation comprises 0.1-50 % by weight oily material, preferably 1-40 %, and 0.5-20 % by weight emulsifier.

5. Use according to claim 3 or 4, wherein the galactolipid material consists of at least 50 % by weight digalactosyl-diacylglycerols and a remainder of other polar lipids, preferably in an amount of 1.0-5.0 % by weight.

6. Use according to any of claims 3-5, wherein the galactolipid material consists of 50-70 % by weight digalactosyldiacyl-glycerols and 30-50 % other polar lipids.

7. Use according to claim 3 or 4, wherein the galactolipid material is a fractionated oat oil which contains 10-90 % by weight polar lipids and a remainder of non-polar lipids, preferably in an amount of 2.0-10 % by weight.

8. Use according to any of claims 3, 4 and 7, wherein the galactolipid material is a fractionated oat oil which contains 40-60 % by weight polar lipids and a remainder of non-polar lipids.

9. Use according to any of claims 3-8, wherein the active substance is a pharmacologically active substance.

10. Use according to any of claims 3-8, wherein the active substance is a cosmetological substance.

11. Use according to any of claims 3-8, wherein the active substance is a moisturiser.

12. Topical cream base giving an incorporated substance a sustained effect, comprising in % by weight

Oily material	10.0-30.0 %
Galactolipid emulsifier	0.5-5 %
Thickener	2.0-10.0 %
Preservative	0.1-1.0 %
Water	ad 100 %

13. Topical formulation having a prolonged moisturising effect, comprising in % by weight

Glycerol	1.0-5.0 %
Oily material	10.0-30.0 %
Galactolipid emulsifier	0.5-5 %
Thickener	2.0-10.0 %
Preservative	0.1-1.0 %
Water	ad 100 %

14. Topical formulation having a prolonged anti-inflammatory effect, comprising in % by weight

Hydrocortisone	0.5-1.5 %
Oily material	10.0-30.0 %
Galactolipid emulsifier	0.5-5 %
Thickener	2.0-10.0 %
Preservative	0.1-1.0 %
Water	ad 100 %

15. Topical formulation having a prolonged anti-inflammatory effect, comprising in % by weight

Betamethasone	0.01-0.5 %
Oily material	10.0-30.0 %
Galactolipid emulsifier	0.5-5 %
Thickener	2.0-10.0 %
Preservative	0.1-1.0 %
Water	ad 100 %

16. Topical formulation having a prolonged anti-psoriatic effect, comprising in % by weight

13-hydroxy-linoleic acid	0.001-0.1 %
Oily material	10.0-30.0 %
Galactolipid emulsifier	0.5-5 %
Thickener	2.0-10.0 %
Preservative	0.1-1.0 %
Water	ad 100 %

17. Use of a topical formulation according to claim 1 or 2, wherein the incorporated compound is a moisturising compound for the preparation of a medicament for prophylaxis or treatment of atopic dermatitis.

18. Use of a topical formulation according to claim 1 or 2, wherein the compound is a corticosteroid for the preparation of a medicament for treatment of skin inflammation.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 99/00347

A. CLASSIFICATION OF SUBJECT MATTER

IPC6: A61K 9/107, A61K 7/00, A61K 47/00
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC6: A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

WPI, EPODOC, EMBASE, MEDLINE, CAPLUS

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 9520943 A1 (KARLSHAMNS LIPIDTEKNIK AB), 10 August 1995 (10.08.95), page 4, line 20 - page 7, line 11, claims ---	1-15
X	EP 0647443 A1 (L'OREAL), 12 April 1995 (12.04.95), claims --- --------	1-4,9-11

☐ Further documents are listed in the continuation of Box C. ☒ See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" erlier document but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
16 June 1999	03 -07- 1999
Name and mailing address of the ISA/ Swedish Patent Office Box 5055, S-102 42 STOCKHOLM Facsimile No. +46 8 666 02 86	Authorized officer Anneli Jönsson/EÖ Telephone No. +46 8 782 25 00

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 99/00347

Box I **Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)**

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 3-8 (partly), 9
because they relate to subject matter not required to be searched by this Authority, namely:

see next page

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

Box II **Observations where unity of invention is lacking (Continuation of item 2 of first sheet)**

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 98/00347

Remark: Claims 3-8 (partly) 9 are directed to methods of treatment of the human or animal body by surgery or by therapy/ diagnostic methods practised on the human or animal body/Rule 39.1(iv). Nevertheless, a search has been executed for these claims. The search has been based on the alleged effects of the compounds/ composition.

INTERNATIONAL SEARCH REPORT

Information on patent family members

01/06/99

International application No.
PCT/SE 99/00347

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
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INTERNATIONAL SEARCH REPORT

Information on patent family members

01/06/99

International application No.
PCT/SE 99/00347

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CLAIMS

1. Use of a formulation of the oil-in-water emulsion type comprising an oily material, an aqueous phase and a galactolipid material as an emulsifier, as a carrier for the preparation of a topical cream or lotion providing a prolonged local effect of an incorporated pharmaceutically or cosmetically active substance.

2. Use according to claim 1, wherein the formulation comprises 0.1-50 % by weight of oily material and 0.5-20 % by weight of emulsifier.

3. Use according to claim 1 or 2, wherein the formulation comprises 1-40 % by weight of oily material and 0.5-10 % by weight of emulsifier.

4. Use according to any of claims 1-3, wherein the galactolipid material consists of at least 50 % by weight of digalactosyl-diacylglycerols and a remainder of other polar lipids, and constitutes an amount of 1.0-5.0 % by weight of the formulation.

5. Use according to any of claims 1-4, wherein the galactolipid material consists of 50-70 % by weight of digalactosyldiacyl-glycerols and 30-50 % by weight of other polar lipids.

6. Use according to any of claims 1-3, wherein the galactolipid material is a fractionated oat oil which consists of at least 15 % by weight of digalactosyldiacylglycerols and a remainder of other polar and non-polar lipids, and constitutes an amount of 2.0-10 % by weight of the formulation.

7. Use according to any of claims 1-3 and 6, wherein the galactolipid material is a fractionated oat oil which contains 40-60 % by weight polar lipids and a remainder of non-polar lipids.

8. Use according to any of claims 1-7, of a cream base, comprising, in % by weight

Oily material	10.0-30.0 %
Galactolipid emulsifier	0.5-5 %
Thickener	2.0-10.0 %
Preservative	0.1-1.0 %
Water	ad 100 %

9. Use according to any of clains 1-8 for the preparation of a topical cream or lotion, incorporating a moisturiser, especially glycerol, as the active substance.

10. Use according to any of claims 1-9 for the preparation of a medicament for prophylaxis or treatment of atopic dermatitis.

11. Use according to any of claims 1-8 for the preparation of a topical cream or lotion, incorporating a corticosteroid as the active substance, for treatment of skin inflammation.

12. Use according to any of claims 1-8, for the preparation of a topical anti-psoriatic cream or lotion, incorporating 13-hydroxy-linoleic acid as the active substance.